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EDITORIAL COMMENT

Biomonitoring and Biomarker-Guided Therapy

The Next Step in Heart Failure and Biomarker Research*

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In an editorial several years ago surrounding the publication of the BATTLE-SCARRED (NT-proBNP-Assisted Treatment to Lessen Serial Cardiac Readmissions and Death) trial (1,2), I surmised that in the not too distant future, biomarker-guided therapy might allow physicians to personalize heart failure (HF) treatment toward the betterment of patients. Holding up the "biomarker bar" were the natriuretic peptides (NPs). Excellent surrogates for ventricular stretch and volume overload, they appeared ideally suited as a means to drive individual therapy for acute ("wet B-type NP [BNP]") and chronic ("dry BNP") HF (3–5).

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Wet BNP represents acutely synthesized BNP or proBNP that occurs with ventricular stretch from volume overload, and dry BNP represents ventricular remodeling, fibrosis, and end-diastolic stress. Although there has yet to be a large randomized controlled trial of NP-guided therapy for acute HF, there have been a number of studies of NP-guided treatment for HF in the outpatient setting. Although many of these studies have yielded equivocal and often controversial results, it is generally accepted that there is some benefit, especially in those under 75 years of age (6,7). It was my opinion 2 years ago that what many of these studies lacked was the "biomonitoring" necessary to allow aggressive uptitration of therapy in an attempt to actually decrease the NP levels that were supposed to be guiding therapy (8). This, I believe, has been achieved by Januzzi et al. (6) in the PROTECT (Pro-BNP Outpatient Tailored Chronic Heart Failure Therapy) study, in this issue of the *Journal*.

Although PROTECT has the weakness of being a single-center, unblinded study, measurable criteria such as NP level, quality of life, and ventricular function were measured and significantly improved in the NP-guided arm. The investigators are to be congratulated for strong adherence to study protocol with consistent biomonitoring of amino-terminal pro-BNP (NT-proBNP) levels, allowing aggressive therapeutic efforts at NT-proBNP lowering. Thus, since my last editorial, I believe that we can now be confident that lowering NP levels is indeed possible (it happened in PROTECT), is safe (the kidneys still work, the blood pressure is fine), and may lead to more benefits compared with simple nonbiomonitored up-titration of therapies. PROTECT demonstrates the most robust lowering of NT-proBNP concentrations reported to date in any trial, with more than 44% of the "guided" therapy arm achieving goal values. This was reflected in the increased number of office visits and more diligent drug titration in the NT-proBNP–guided arm, something quite different from prior trials.

One possible limitation of the PROTECT trial is the generalizability of its results. The "intervention" was not limited to providing to the "active" arm investigators with NP levels (biomonitoring). It also comprised an intensive, proactive implementation of treatment optimization steps, eventually prompted or encouraged by reminders from the study organization and steering committee. This kind of proactive biomonitoring may be possible only within structured disease management programs. The patients were also younger than in many other studies and therefore may have tolerated medication increases better than older patients. Finally, the sample size was small, and there was a relatively brief duration of follow-up. Therefore, although the concept is proven, extrapolation to the real world and daily practice must still be demonstrated.

Toward a New Definition of the "Ideal" Biomarker

Morrow and de Lemos (9) proposed 3 criteria required for a biomarker to be clinically useful. First, the assay should be precise, accurate, and rapidly available to clinicians at a relatively low cost. Second, the biomarker must provide additional information that is not surmised from clinical evaluation. Last, the absolute measured value should help in clinical decision making. The results of PROTECT allow a reasonable revision that takes into account both biomarker-guided therapy and biomonitoring during treatment (Table 1).

The following are 2 still hypothetical examples in the setting of acute HF whereby one might be able to take advantage of biomarkers that are surrogates of abnormal physiology or biochemistry, allowing us to potentially treat with a specific agent that improves outcomes as levels of that biomarker decrease.

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Table 1 The Ideal Biomarker

2007	2011
Sensitive and specific	Either highly sensitive (diagnosis) or highly specific (treatment effect)
Reflects disease severity	Reflects abnormal physiology or biochemistry
Correlates with prognosis	Prognosis is most meaningful if level is clinically actionable
Should aid in clinical decision making	Should be used as a basis for specific "biomarker-guided therapy"
Level should decrease after effective therapy	"Biomonitoring" during treatment is an effective surrogate of improvement

High-sensitivity troponins. Studies have demonstrated that patients with acute decompensated HF sometimes have troponin elevations that are associated with poor prognosis (10–12). Representing, in part, myocyte necrosis from subendocardial ischemia, elevated troponins in acute HF are useful only for risk stratification. The advent of new troponin assays capable of detecting troponins in the range of nanograms per liter represents a new opportunity (13). In a recent trial in which serial sampling of high-sensitivity troponin I in acute HF was obtained, 2 distinct phenotypes were seen (12). Although admission high-sensitivity troponin I levels were similar between all patients, those with rapidly rising levels during hospitalization had worse outcomes than those who had little or no increases. One could conceivably "target" such an increase in troponin in acute HF with agents that specifically affect subcellular myocardial ischemia and subsequent myocyte necrosis (e.g., ranolazine). It may therefore become reasonable to believe that an acute intervention that protects the heart from cell injury (as targeted in patients with continuous increases in high-sensitivity troponin) may have an effect on long-term outcomes. Figure 1 demonstrates a purported effect of such a drug compared with placebo, mitigating the troponin elevation and perhaps improving morbidity and mortality.

Copeptin. In patients with HF, increased arginine vasopressin (AVP) concentrations are associated with more severe disease, making AVP an attractive target for therapy. However, AVP is difficult to measure because of its in vitro instability and rapid clearance. Copeptin, the C-terminal segment of pre-provasopressin, is a stable and reliable surrogate biomarker for serum AVP concentrations (14). Copeptin was measured as part of the BACH (Biomarkers in Acute Heart Failure) study (15). Data from secondary analysis of the BACH study revealed increased 90-day mortality, readmission, and emergency department visit rates in patients with elevated copeptin levels. Although patients with low sodium and elevated copeptin were at significantly increased risk for 90-day mortality, copeptin levels were independent of sodium levels (16). Therefore, copeptin may be a better surrogate for AVP elevation and a sensible pharmacophenomic that may be specifically targeted by AVP antagonists in HF. Although AVP antagonists have been used to treat hyponatremia in the general population with encouraging results, efforts to use them in patients with HF were not as successful (17). The ACTIVATE (Acute Heart Failure Patients With High Copeptin Levels Treated With Tolvaptan Targets Increased AVP Activation for Treatment Efficacy) trial is a multicenter study that will randomize patients admitted for acute HF to tolvaptan versus placebo on the basis of activation of the AVP axis (copeptin). The study is set to begin in 2012 and represents one of the first cases of partnering between the pharmaceutical (Otsuka American Pharmaceutical, Inc., Rockville, Maryland) and diagnostic (Brahms-Thermo Fisher, Waltham, Massachusetts) industries. If the study is successful, it would not be farfetched to "biomonitor" patients with chronic HF with copeptin measurements and provide intermittent tolvaptan therapy in those whose levels have risen from baseline.

Conclusions

This editorial does not condone using biomarkers as surrogate end points for phase 3 clinical trials. That pathway has led to disaster in a number of trials (18). What it does suggest is that undertaking and completing studies that use a rigorous combination of biomarker guidance and biomonitoring with solid surrogates such as the NPs can lead to improvement in patient care. Kudos to Januzzi et al. (6) for a valiant effort in this regard. The just completed HABIT (Heart Failure Assessment With B-Type Natriuretic Peptide in the Home) study is testing the feasibility of finger-stick NP tests in the home, possibly negating some of the "burdensome" patient office visits. Although the NPs come close to the new proposed definition of an ideal marker, other biomarkers are sure to follow. Those that are successful will likely either be sensitive diagnostic or specific prognostic markers. The validation of some biomarkers as

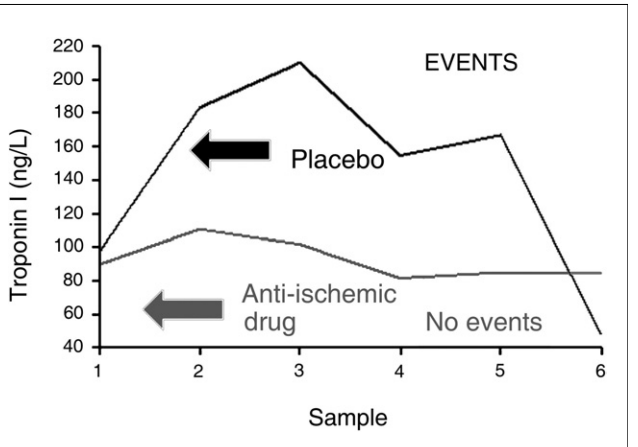

Figure 1 Hypothetical Trial Using Troponin to Guide Treatment in Acute Heart Failure

In a hypothetical study, patients with acute heart failure and either elevated high-sensitivity troponin or early rising troponin would be randomized to an anti-ischemic drug versus placebo. The figure speculates that successful treatment will mitigate troponin elevation, while placebo would not. Adapted from Xue et al. (11).

physiologic or biochemical surrogate markers that can be used to both guide therapy and monitor the effects of that therapy may lead to a better segmentation of the HF syndrome into individual phenotypes (so-called pharmacophenomics) on the basis of the likelihood of response to specific therapies. Markers of acute kidney injury (neutrophil gelatinase–associated lipocalin) and myocyte necrosis (high-sensitivity troponins), along with methods to assess tissue water, are likely to facilitate this segmentation. This is typically what personalized medicine is, as opposed to "one size fits all" medicine, thus far the basis of our current management of HF.

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